J. Radiat. Res., 47, 49–59 (2006)

Regular Paper

A Pathology Study of Malignant and Benign Ovarian Tumors Among Atomic-Bomb Survivors – Case Series Report –

Kouki INAI[1], Yukiko SHIMIZU[2]*, Kioko KAWAI[3], Masayoshi TOKUNAGA[2], Midori SODA[2], Kiyohiko MABUCHI[4], Charles E. LAND[4] and Shoji TOKUOKA[5]

Ovarian tumor/Histological type/Ionizing radiation.

The present article describes the series of incident primary ovarian tumors in the Life Span Study (LSS) cohort of the Radiation Effects Research Foundation, with particular emphasis on case ascertainment and characterization of histological features of the tumors. We identified 723 ovarian tumors (260 malignant, 463 benign) in 648 individuals of about 70,000 female LSS subjects; 71 cases had more than one ovarian tumor. We histologically confirmed 601 tumors (182 malignant, 419 benign tumors). The most frequent histological type was common epithelial tumor (90.7% for malignant and 59.7% for benign tumors). The distributions of ovarian tumors by histological type were similar to those from other studies. Among malignancies, the frequency of common epithelial types relative to other tumor types increased with radiation dose ($p = 0.02$). Among benign tumors, the relative frequency of sex-cord stromal tumors increased with radiation dose ($p = 0.04$). The women with mucinous cancer had better survival than those with serous cancers ($p = 0.03$). Within tumor types, there was no consistent pattern of survival by radiation dose. Variations in histological types of ovarian tumors in response to radiation dose, suggested by the case series data need to be followed up by population-based incidence analysis.

INTRODUCTION

Tumors of the ovary are characterized by a variety of histologic features and prognosis. The majority of ovarian tumors are of celomic epithelial origin while germ cells and sex-cord stromal tumors are much less frequent. Epithelial carcinomas approximate the over all incidence rates of ovarian cancer in many countries. Japanese women reportedly have lower incidence rates of ovarian cancer, especially of epithelial types, than US or European women.[1,2)] While ovarian cancer incidence rates in the US and Europe have generally been stable during the past several decades,[3)] increasing trends have been reported for ovarian cancer mortality and incidence in Japan.[4,5)] Repeated stimulation of the ovarian epithelium has been suspected to be a predisposing factor for malignant transformation of ovarian tissue.[6)] This is supported by an increased risk of ovarian cancer associated with nulliparity, and a reduced risk associated with pregnancy, lactation and oral contraceptive use.[7)]

In the follow-up of the Life Span Study (LSS) cohort of atomic bomb survivors conducted by Atomic Bomb Casualty Commission (ABCC) and its successor, Radiation Effects Research Foundation (RERF), we observed an excess risk of ovarian cancer associated with radiation exposure for mortality[8)] and incidence[9)]studies. Our previous pathology study[10)] of ovarian tumors involved 194 subjects with malignant tumors of the ovary diagnosed in this cohort between 1950 and 1980. The study provided evidence of a significant dose response for ovarian malignancies. Analysis of 106 subjects with benign ovarian tumors detected at autopsy also showed the proportion of benign tumor cases to increase significantly ($p < 0.05$) with increasing dose, but the distribution of histological types did not vary significantly with radiation dose. Epidemiological data on ovarian cancer risk on other irradiated populations are generally limited, and are largely reported from studies of medically exposed populations. Evidence of radiation-related excess risk of ovarian cancer

*Corresponding author: Phone: +81-82-261-3131,
Fax: +81-82-262-9768,
E-mail: shimizu@rerf.or.jp

[1]Department of Pathology, Division of Medical Intelligence and Informatics, Programs for Applied Biomedicine, Graduate School of Biomedical Sciences, Hiroshima University, Hiroshima, Japan; [2]Department of Epidemiology, Radiation Effects Research Foundation, Hiroshima and Nagasaki, Japan; [3]Department of Pathology, Nagasaki General Health Center, Nagasaki, Japan; [4]Radiation Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, MD, USA; [5] Consultant, Radiation Effects Research Foundation.

Abbreviation used: LSS (Life Span Study); RERF (Radiation Effects Research Foundation); NIC (Not In City); UNK (Unknown); ICD (International Classification of Diseases); WHO (World Health Organization)

was found in long-term survivors among patients given high-dose radiotherapy for cervical cancer[11–13] and in women irradiated for benign genital organ lesions[14,15] but not in patients treated with x-rays for ankylosing spondylitis.[16,17]

This report extends pathology reviewed-based study through 1988. The focus of the present study, as with the previous pathology studies,[10] is on intensive pathology review of benign and malignant ovarian tumors including possibly unrecognized cases not previously accepted or even not reported to the tumor registries, classification by malignancy and histological subtype, and analysis for prognosis and variation by age and radiation dose. Thus, the present study provides validation information for tumor registry diagnoses, histological subtypes, and information on benign tumors not available from the tumor registry. This article describes the case series, with particular emphasis on characterization of histological features of the tumors. Since a large number of subjects (over 54%) in the LSS cohort have little (i.e., at < 5 mSv) or no exposure to atomic bomb radiation, this cohort is also a valuable source of information on general histological characteristics of ovarian tumors in Japan.

MATERIALS AND METHODS

Initial case ascertainment

The LSS cohort includes about 70,000 women, of whom 54,694 were exposed to the bombings and another 15,385 (the so-called not- in-city (NIC) subset) were selected during 1951–1953 from contemporary residents of the city of Hiroshima or Nagasaki who were not present in the city at the time of the bombings. Cases in the LSS cohort were ascertained by linkage to the tumor and tissue registries in Hiroshima and Nagasaki. The Hiroshima and Nagasaki tumor registries are population-based registries established in 1957 and 1958, respectively. Reportable tumors for the tumor registries are all malignant and selected benign tumors; until 1975, the latter have included benign ovarian tumors. However, both benign and malignant tumors are reported to the tissue registries. The tissue registries, started in 1973, are pathology-based registries that collect pathology diagnoses and tumor tissue slides for histologically diagnosed tumors in Hiroshima and Nagasaki.

In addition, autopsy and surgical pathology records at RERF were accessed. Large numbers of benign ovarian tumors in the present study were ascertained from these pathology records. The autopsy program was active at ABCC/RERF between 1948 and 1987. Prior to 1961, autopsies were performed primarily on referrals from local physicians and hospitals and the selection reflected ABCC's interests, for example, deaths from leukemia and malignancies. In the procurement program started in 1961, attempts were made to obtain a representative sample by ascertaining deaths among the LSS and other cohorts from a variety of sources in the Hiroshima and Nagasaki community. A large number of autopsies (about 8,200 in total) were carried out at ABCC/RERF in the LSS cohort. The ABCC the surgical pathology program was active from the late 1950s through the late 1960s; tissues specimens and blocks for tumor and other lesions were sent from local hospitals to ABCC.

The current study also used clinical records maintained at RERF and death certificates for deceased members obtained for the mortality follow-up of the LSS cohort since 1950. The present study includes primary tumors during 1950-88.

Pathology review

In the initial screening, case records for all tumors initially selected were closely inspected by one of the pathologist-panel members (MT), who excluded any with diagnoses clearly inconsistent with ovarian tumor. For the remainder, relevant tissue slides with pathology reports, if available, were reviewed by the panel of two pathologists (K.I. and K.K.) and a histological diagnosis was given. The radiation exposure doses for cases were unknown to the pathologists. Tumor types were decided according to the classification by the World Health Organization.[18] The histological classification compiled by the Japanese Society of Obstetrics and Gynecology and the Japanese Society of Pathology[19] was also used for reference. When the two panel members did not agree on histological diagnosis or type, or when a diagnosis made by the panel did not agree with the diagnosis previously given by a hospital pathologist, the panel met again to discuss and review the materials to reach a final consensus diagnosis. Thus, possible tumors were accepted or excluded on the basis of review of histological slides by the present authors. When pathology records were available but slides of the purported primary ovarian tumor were not available for review, pathology diagnoses made by hospital pathologists were accepted or rejected based on review by the current pathology panel. The remaining possible tumors, for which neither histological samples nor pathology records were available, were those with information from clinical records or death certificate information only, and these were accepted on the basis of the results of the initial screening review (MT).

Statistical Analysis

Inferences regarding proportional frequencies of different histological types of ovarian tumors were made with respect to variation by radiation dose, city, age at diagnosis, and year of diagnosis. The analyses were performed by modeling the binomial odds, fitted by maximum likelihood, using the GMBO algorithm from the EPICURE package[20] of statistical programs for analyses of epidemiologic data. It means that logistic regression analyses were performed. The natural logarithm of the odds, p/(1-p), where p is the relative frequency of the diagnosis of interest, was modeled as a linear parametric function of the exposure variables, within strata

defined by cross-classification of city, age at diagnosis, and year of diagnosis:

$$\log(p_i/(1- p_i)) = \alpha_i + \sum \beta_j X_j.$$

Here, the subscript i corresponds to stratum and the subscript j identifies the exposure variables, which are radiation dose and two indicator variables, one for exposure status and the other for availability of the dose estimate among the exposed.

Survival time, from diagnosis of ovarian tumor through 2001, was evaluated as a function of tumor type and/or radiation dose, by proportional hazards methods using the PEANUTS algorithm, also from the EPICURE package. Survival time was defined as time from tumor diagnosis to death, without regard to cause, or specifically from diagnosis to death from ovarian cancer, in which case death from other causes was treated as loss to follow-up.

Radiation Dose Estimates

Individual radiation dose estimates were obtained from the recently revised RERF Dosimetry System 2002 (DS02).[21] DS02 provides individual dose estimates for gamma rays and neutrons based on individual exposure history information. As in other RERF studies, individual weighted dose, expressed in sieverts (Sv), was calculated for each survivor as the weighted sum of gamma dose and neutron dose in grays (Gy), with neutron dose assigned a weight of 10.

Ethical issues

This study was approved by the Human Investigation Committee at RERF in 1992.

RESULTS

A total of 1,964 conditions considered as possibly consistent with ovarian tumor (i.e., with ICD-9: 183.0, 183.8, 198.6, 220, 236.2, 239.5), in 1,733 cohort members, were selected for initial screening. Of these conditions 478 (404 identified from clinical records and 74 from death certificates) were excluded because the diagnoses were clearly inconsistent with ovarian tumors. Sixty-seven of the remaining conditions were accepted based on the initial screening given only clinical record (41 in 37 persons) or death certificate (26 in 26 persons) information. Relevant tissue slides with pathology reports were available for 932 conditions. Six hundred and one (601) conditions in 535 persons were accepted as tumors and 331 in 177 persons were rejected on the basis of review of histological slides by the present authors. The majority of rejected lesions were cysts without neoplasm (71%), metastatic tumors from other organs and a few ovarian tumors outside the timeframe of the present study, i.e., diagnosed before 1950 or after 1988. Pathology records, but not tissue slides, were available for 487 lesions (in 480 persons), of which 55 (in 50 persons) were accepted as tumors and 432 (in 430 persons) were rejected (absence of primary ovarian tumor, 54%, metastatic tumor, 42%, and other, 4%).

In all, 723 ovarian tumors in 648 women were accepted. Of these, 601 (83.1%) were histologically confirmed as ovarian tumors by the present investigators, and 55 (7.6%) were accepted on the basis of pathologists'reports for which the original tissue slides were unavailable to the panel. In the absence of histological information, 41 cases (5.7%) with clinical diagnoses and 26 cases (3.6%) with death certificate diagnoses only were accepted on the basis of record review (Table 1).

Of the 723 ovarian tumors 260 (36.0%), in 232 women, were malignant (including 37 of borderline malignancy) and 463 (64.0%), in 345 women, were benign. Mean ages at diagnosis were 61 and 58 years for malignant and benign tumors, respectively. The distributions by city of malignant and benign cases were both roughly in agreement with the distribution of female LSS sample members in the two cities: 34% of the malignant tumors and 29% of the benign tumors occurred among the 31% of female LSS subjects from Nagasaki. (However, birthdates for female Hiroshima LSS subjects were on the average 3.6 years earlier than for female Nagasaki subjects, which would tend to increase the baseline rate (i.e., unrelated to radiation exposure) of ovarian tumors among Hiroshima compared to Nagasaki survivors.

There were 182 malignant tumors or borderline malignancies (malignancies 145, borderline malignancies 37) histologically confirmed by the present investigators. Of the total, 165 (90.7%) were classified as common epithelial tumors, 12 (6.6%) as sex-cord stromal tumors and the remaining 5 cases (2.7%) as germ cell tumors. The common epithelial tumors were predominately serous type carcinoma (53.3%) and mucinous type carcinoma (24.2%) (Table 2). The most frequent benign tumors were common epithelial tumor (59.7%), followed by germ cell tumor (27.9%) and sex-cord stromal tumor (11.9%) (Table 2). Serous tumors were the predominant type (61.2%) among common epithelial tumors, followed by mucinous tumors (31.2%). Fibroma was the predominant type (80.0%) among sex-cord stromal tumors, while the vast majority of germ cell tumors (96.6%) were mature cystic teratoma.

Distribution of histological type by radiation exposure

Histologically confirmed primary ovarian cancers, including tumors of borderline malignancy, are distributed in Table 3 by morphological type, exposure group and, among the exposed, by estimated DS02 ovarian dose. There were 40 malignant tumors in the non-exposed (NIC) group, 129 among exposed persons with dose estimates, and 13 with unknown dose. The proportion (relative frequency) among malignant tumors of common epithelial tumors was 91% overall, 85% among the NIC and 100% among women exposed to 0.1 Sv or more. By formal statistical analysis: in

Table 1. Incident primary ovarian tumors in the Life Span Study samples, 1950–88: Characteristics of the case series

Total tumors		**723**	**(100%)**
Diagnostic confirmation	Histology review by panel	601	83.1
	Histologic diagnosis; no histology review by panel	55	7.6
	Clinical diagnosis	41	5.7
	Death certificate only	26	3.6
City	Hiroshima	499	69.0
	Nagasaki	224	31.0
Year of diagnosis	< 1958	48	6.6
	1958 – 1972	322	44.5
	1973 – 1988	353	48.8
Age at diagnosis	<50	235	32.5
	50–59	120	16.6
	60–69	137	18.9
	70+	231	32.0
Tumor behavior	Malignant	260	36.0
	Benign	463	64.0

Table 2. Distribution of histologically confirmed primary ovarian tumors by histological type, Life Span Study cohort, 1950–1988

	Malignant*		**Benign**	
Tumor histology	**Number of tumors**	**%**	**Number of tumors**	**%**
Common epithelial tumors	**165**	**90.7**	**250**	**59.7**
Serous tumors	88		153	
Mucinous tumors	40		78	
Endometrioid tumors	15		2	
Clear cell tumors	13		0	
Brenner tumors	0		17	
Undifferentiated carcinoma	5		–	
Unclassified epithelial tumors	4		0	
Sex-cord stromal tumors	**12**	**6.6**	**50**	**11.9**
Granulosa cell tumors	10		–	
Thecoma	–		9	
Fibroma	–		40	
Fibrosarcoma	2		–	
Sclerosing stromal tumors	–		1	
Germ cell tumors	**5**	**2.7**	**117**	**27.9**
Mature cystic teratoma	–		113	
Mature cystic teratoma with malignant transformation	4		–	
Struma ovarii	–		4	
Carcinoid	1		–	
Soft tissue tumors	**0**		**2**	**0.5**
Hemangioma	–		1	
Leiomyoma	–		1	
Total	**182**	**100.0**	**419**	**100**

*: Borderline malignancies of 37 tumors are included

terms of fitted binomial odds, the proportion of common epithelial tumors (relative frequency), adjusted for age at diagnosis, city, and calendar year, increased significantly with increasing dose ($p = 0.02$ for linear trend) among the exposed with estimated doses. Thus, ovarian cancer risk was dominated by common epithelial tumors, especially among the exposed subjects, compared to sex-cord stromal tumors and germ cell tumors. Among common epithelial tumors the relative frequency of mucinous tumor tend to decrease with radiation dose though not statistically significant. It implies that radiation risk of nonmucinous tumors might be higher than that of mucinous tumor.

There was non-homogeneity in distribution of type of benign tumors by radiation dose interval ($p < 0.01$)(Table 4) and, in particular, the relative frequency of sex-cord stromal tumor, adjusted for age, city, and year, increased with increased radiation dose ($p = 0.04$). The proportion of serous tumor among common epithelial tumors tends to increase with radiation dose ($p = 0.09$), and that of the mucinous tumor decreases with radiation dose ($p < 0.01$). It implies that if the risk of benign ovarian tumor increases with radiation dose, the radiation risk of sex-cord stromal tumor is higher than that of common epithelial tumor and germ cell tumor and that among common epithelial tumors, the radiation risk of serous tumor is higher than that of mucinous tumor.

Distributions of benign and malignant tumor cases by

Table 3. Histologically confirmed primary ovarian cancers by radiation dose and histological type, Life Span Study cohort, 1950–1988

Histologic type of tumor	Total	NIC	Ovary dose (Sv)						Regression coefficient* of radiation dose at 1Sv	
			<0.005	0.005-	0.10–	0.50–	1.00+	Unk.		
Common epithelial tumors	**165** (91%)	**34** (85%)	**55** (90%)	**33** (92%)	**18** (100%)	**6** (100%)	**8** (100%)	**11** (85%)	**21.2**	**P = 0.02**
Serous adenocarcinoma	88	21	33	14	9	3	5	3	–0.05**	P > 0.5
Mucinous adenocarcinoma	40	7	15	8	4	2	0	4	–0.89**	P = 0.26
Sex–cord stromal tumors	**12**	**5**	**4**	**1**	**–**	**–**	**–**	**2**	**–19.8**	**P = 0.11**
Germ cell tumors	**5**	**1**	**2**	**2**	**–**	**–**	**–**	**–**	**– 9.6**	**P = 0.22**
Total	**182** (100%)	**40** (100%)	**61** (100%)	**36** (100%)	**18** (100%)	**6** (100%)	**8** (100%)	**13** (100%)		

*: adjusted for age at diagnosis, city, and year
**: relative frequency among common epithelial tumors.

Table 4. Histologically confirmed primary benign ovarian tumors by radiation dose and histological type, Life Span Study cohort, 1950–1988

Histologic type of tumor	Total	NIC	Ovary dose (Sv)						Regression coefficient* of radiation dose at 1 Sv	
			<0.005	0.005-	0.10–	0.50–	1.0+	Unk.		
Common epithelial tumors	**250** (60%)	**52** (60%)	**60** (56%)	**72** (66%)	**34** (61%)	**14** (47%)	**11** (61%)	**7** (64%)	**0.06**	**P > 0.5**
Serous adenoma	153	21	38	53	22	7	10	2	0.64**	P = 0.09
Mucinous adenoma	78	24	21	16	8	4	–	5	–1.47**	P < 0.01
Sex-cord stromal tumors	**50** (12%)	**9** (10%)	**10** (9%)	**12** (11%)	**8** (14%)	**7** (23%)	**4** (22%)	**–** (–)	**0.83**	**P = 0.03**
Germ cell tumors	**117** (28%)	**26** (30%)	**37** (34%)	**24** (22%)	**14** (25%)	**9** (30%)	**3** (17%)	**4** (36%)	**–0.81**	**P = 0.10**
Other tumors	**2** (0%)	**–** (–)	**1** (1%)	**1** (1%)	**–** (–)	**–** (–)	**–** (–)	**–** (–)		
Total	**419** (100%)	**87** (100%)	**108** (100%)	**109** (100%)	**56** (100%)	**30** (100%)	**18** (100%)	**11** (100%)		

*: adjusted for age at diagnosis, city, and year
**: relative frequency among common epithelial tumors.

Table 5. Number of malignant and benign tumors, and proportion of benign tumors among total tumors

Source of diagnosis		Total	NIC	Ovary dose (Sv)						Regression coefficient* of radiation dose at 1 Sv	
				<0.005	0.005–	0.10–	0.50–	1.0+	Unk.		
Autopsy	Malignant	7	3	2	1	–	–	1	–		
	Benign	145	19	37	49	27	8	2	3		
	Proportion of benign tumor	(95.40%)	(86.4%)	(94.7%)	(98.0%)	(100.0%)	(100.0%)	(66.7%)	(100.0%)	–5.1	P = 0.26
Others	Malignant	175	37	59	35	18	6	7	13		
	Benign	274	68	71	60	29	22	16	8		
	Proportion of benign tumor	(61.0%)	(64.8%)	(54.6%)	(63.2%)	(61.7%)	(78.6%)	(69.6%)	(38.1%)	0.88	P = 0.03
Total	Malignant	182	40	61	36	18	14	8	13		
	Benign	419	87	108	109	56	30	18	11		
	Proportion of benign tumor	(69.7%)	(68.5%)	(63.9%)	(75.2%)	(87.5%)	(68.2%)	(69.2%)	(45.8%)	0.67	P = 0.08

*: adjusted for age at diagnosis, city, year, clinical sample, and source of diagnosis

exposure and radiation dose are tabulated separately for autopsy and non-autopsy in Table 5. Less than 5% of the autopsied cases had malignant tumors, compared to 39% of non-autopsied cases. Among non-autopsied cases exposed to the bombings and with dose estimates, the proportion of benign cf. malignant cases increased significantly ($p = 0.03$) with increasing dose after stratification by clinical sample, year, city, and age at diagnosis, whereas among autopsied cases the increasing trend of the proportion of benign cf. malignant cases was not significant ($p = 0.26$). Overall, after stratification by source of diagnosis as well as the other stratification variables, the trend was just marginaly statistically significant ($p = 0.08$), with an estimated odds ratio for benign vs. malignant tumor of 2.0 (95%CI: 0.89-4.3) at 1 Sv compared to 0 Sv. Given that ovarian cancer risk has been shown to increase with radiation dose, this finding suggests that the same is true for benign ovarian tumors and that the association with radiation dose may be at least as strong as that for malignant tumors.

Age distribution and temporal trends

Among malignant tumors including borderline malignancy age at diagnosis for common epithelial tumors tended to be younger than that for combined germ cell and sex-cord stromal tumors. This difference is supported by formal statistical analysis: in terms of fitted binomial odds (see Methods), the relative frequency of common epithelial tumors decreased significantly ($p = 0.05$) with increasing age (data not shown). Among benign tumors common epithelial tumors tended to be diagnosed at older ages than other tumor types , whereas germ cell tumors tended to be diagnosed at younger ages. The relative frequency of common epithelial tumors increased significantly ($p < 0.001$) and the relative frequency of germ cell tumors decreased ($p < 0.001$) with increasing age (data not shown).

As for the time trend, the proportion of common epithelial tumors among all ovarian tumors did not change over time (data not shown). However, the proportions of subtypes of common epithelial tumors changed by time. Among both malignant and benign tumors, the proportion of serous type tumors decreased significantly with time ($p = 0.02$ for malignant; $p < 0.001$ for benign) while that of mucinous and other common epithelial tumors increased .

Prognosis of ovarian tumors

Prognosis was examined for 493 persons who were alive at diagnosis of ovarian tumors. Of 281 deaths from the time

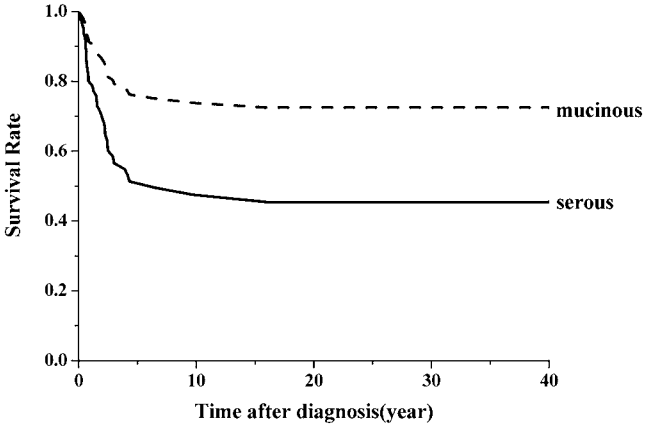

Fig. 1. Comparison of survival curves (ovary cancer) between serous and mucinous malignant ovarian tumors

of diagnosis through 2001, 118 were from ovarian cancer. Survival curves for all causes of death, adjusted for age at diagnosis, city, and radiation dose, were compared between serous and mucinous cancers. There was a significant apparent survival advantage (all causes of deaths) for mucinous compared to serous cancers ($p = 0.03$), and the difference was marked in the analysis restricted to mortality from ovarian cancer (Fig. 1). Within tumor types survival did not vary consistently by radiation dose(data not shown).

DISCUSSION

The present study was intended to provide an extended ascertainment of ovarian tumors beyond those regularly reported to the tumor and tissue registries in Hiroshima and Nagasaki, and to compare the current findings with our previous series.[10] About 20% of the ovarian cancer cases (both malignant tumors and borderline malignancies) included in the early series turned out to be neither malignant tumors nor borderline malignancies in the present study. This high false positive rate may have developed because the 1st screening as conducted in the current study had not been performed previously. In the present 1st screening, one of the pathologist-panel members inspected case records for all tumors initially selected and excluded any with diagnoses clearly inconsistent with ovarian tumor. Histologically-reviewed cases showed good agreement in both early and present studies. About 20% of the ovarian cancer cases (only malignant tumors but not borderline malignancies) in Thompson's the tumor registry-based study were not malignant tumors, and one third of those tumors were borderline malignancies in the present study. Also, on the basis of present study, 10% and 5% of ovarian cancer cases that might have been identified by a more thorough ascertainment process were missed by our previous study[10] and the Thompson study,[9] respectively. Ascertainment of benign ovarian tumors was not limited to autopsy cases as in the earlier series; however, with screening of a wider variety of possible ovarian tumors among autopsy cases and the resources of a much improved tumor registry, the number of histologically confirmed tumors eligible under the criteria for the previous study was increased by 60%, while 11% of the original tumors were rejected by the present investigators.

In our previous study,[10] which was based on 128 malignant tumors and 98 benign tumors, the distribution of histological types of both malignant and benign tumor of the ovary did not vary significantly with radiation dose based on simple chi-squired test, although the proportion of clear cell carcinoma tended to increase with dose. In the present study based on 182 malignant tumors and 419 benign tumors, we found that the relative frequency of common epithelial tumors to other malignant tumor types increased with radiation dose ($p = 0.02$). This means that the risk of common epitherial tumor is higher than those of sex-cord stromal tumors and germ cell tumors when risk of ovarian cancer exist. The reasons suspected for this are that cancer development is associated with mutation induced during repair process of damaged ovarian epitherial tissues at each time of ovulation, and that radiation increases the rate of mutation induced during the repair process of ovarian epitherial tissues. Among benign tumors the relative frequency of sex cord stromal tumors increased with radiation dose ($p < 0.04$). The proportion of serous tumor among common epithelial tumors tends to increase with radiation dose ($p = 0.09$), and that of the mucinous tumor decreases with radiation dose ($p < 0.01$). With respect to the distribution of ovary tumor cases, differences between the previous and present results might have resulted not only increased number of cases in the present study but also use of different statistical methods. The present findings suggest variation of histological specificity in ovarian tumors by radiation dose; however, this question is better addressed in the population-based analysis which will appear in the companion paper. However, it has been reported that reproductive factors , which are important risk factors of ovarian tumors, are more strongly associated with the risk of nonmucinous tumors than that of mucinous tumors.[22] It is also highly possible that the association of radiation with ovarian tumors differs by histologic type.

It is known that autopsy rates in the LSS population are influenced by radiation dose, membership in the clinical subsample of the LSS population, and exposure in Hiroshima cf. Nagasaki.[23] Deceased LSS participants with higher radiation doses are more likely to have been autopsied. Therefore, to the extent that tumor cases have been ascertained at autopsy or from archival autopsy materials that would not otherwise have been discovered, an association of tumor incidence rate in the population-based analysis with radiation dose in the LSS would exist even in the absence of a true association. However, the emphasis in the present study was on relative frequencies of different histological subtypes by radiation dose. Detection of specific types of ovarian tumor among autopsied subjects is unlikely to be correlated with radiation exposure.

Table 5 suggests that the risk of ovarian benign tumor was higher than that of ovarian cancer, when association existed between ovarian cancer and radiation. Studies of effects of A-bomb radiation on the risk of benign tumors are rare because of the difficulty of benign tumor case ascertainment. However, the present study at least suggests the possibility of a relationship between radiation exposure and benign tumor. The reasons why the risk of benign tumors appeared higher than that of malignant tumors are unknown, but one might be that the detection biases of benign tumors at high doses were not fully excluded based only on adjustment for autopsy.

It is known that the incidence of ovarian cancer among Japanese residents differs from those reported in western

countries.[1,2] Tables 6 and 7 compare percentage of both malignant and benign tumor cases by histological type in this study with recent data obtained domestically and abroad.[1,2,24–29] With regard to malignant tumor cases, Table 6 shows that the percentage of common epithelial tumors is overwhelmingly higher than that of two other tumor groups, sex-cord stromal tumors and germ cell tumors, in the data of LA County-USC, as well as those of Nagoya, Juntendo and Tohoku Universities.[24–29] That is to say, among populations in both Japan and the United States, a majority of ovarian malignant tumors are common epithelial tumors, many of which take the form of serous adenocarcinoma. The distribution of ovarian cancers by histogenesis in the present study, however, slightly differs from the other Japanese populations. The proportions of germ cell tumors, and especially that of dysgerminoma, are higher in the other Japanese populations than in the current atomic bomb survivors. This may reflect the fact that the LSS population is a fixed, and there-

Table 6. Primary ovarian cancers by histologic type: Current series versus three other series in Japan and a series in United States

Tumor histology	Number of tumors (%)				
	Current study[a]	Nagoya[a,b]	Tokyo[a,c]	Miyagi[d]	Los Angeles[a,e]
Common epithelial tumors	**165 (90.7)**	**149 (69.6)**	**87 (70.7)**	**41 (78.8)**	**154 (85.6)**
Serous adenocarcinoma	88	73	37	13	78
Mucinous adenocarcioma	40	20	11	7	17
Endometrioid adenocarcinoma	15	26	6	4	20
Clear cell adenocarcinoma	13	25	–	11	7
Mixed epithelial tumor	–	1	3	–	7
Carcinoma	9	4	30	6	25
Sex-cord stromal tumors	**12 (6.6)**	**15 (7.0)**	**4 (3.3)**	**1 (1.9)**	**13 (7.2)**
Granulosa cell tumors	10	12	3	1	10
Fibrosarcoma	2	–	–	–	–
Sarcomatoid androblastoma	–	3	1	–	3
Germ cell tumors	**5 (2.7)**	**48 (22.4)**	**30 (24.4)**	**10 (19.2)**	**12 (6.7)**
Dysgerminoma	–	14	14	3	5
Endodermal sinus tumor	–	11	–	2	1
Embryonal carcinoma	–	–	8	–	–
Polyembryoma	–	1	–	2	–
Choriocarcinoma	–	–	–	1	–
Immature teratoma	–	11	4	2	2
Mature cystic teratoma with malignant transformation	4	7	4	–	4
Carcinoid	1	4	–	–	–
Gonadoblastoma	**–**	**1 (0.5)**	**–**	**–**	**–**
Others	**–**	**1 (0.5)**	**2 (1.6)**	**–**	**1 (0.6)**
Total	**182 (100.0)**	**214 (100.0)**	**123 (100.0)**	**52 (99.9)**	**180 (100.1)**

[a] Cases of borderline malignancy were included.
[b] Patients treated at Nagoya University Hospital during 1965–1988; histologically reclassified cases, Nakashima.[27]
[c] Patients treated at Juntendo University Hospital during 1967–1977; histologically reclassified cases, Ishi.[28]
[d] Histologically reviewed data including cases of borderline malignancy from the Tumor Registry of Miyagi Prefecture during 1969–1977, Sasano.[29]
[e] Patients treated at the Los Angeles County–University of Southern California Medical Center during 1975–1985; histologically reclassified cases, Kooning.[26]

Table 7. Primary benign ovarian tumors by histologic type: Current series versus three other series in Japan and a series in United States

Tumor histology	Number of tumors (%)				
	Current study	Nagoya[a]	Tokyo[b]	Sendai[c]	Los Angeles[d]
Common epithelial tumors	**250 (59.7)**	**275 (44.4)**	**346 (59.3)**	**111 (38.9)**	**245 (37.7)**
Serous adenoma	153	132	174	50	163
Mucinous adenoma	78	130	65	55	75
Endometrioid adenoma	2	–	105	4	–
Brenner tumor	17	7	2	2	7
Mixed tumor	–	6	–	–	–
Sex-cord stromal tumors	**50 (11.9)**	**49 (7.9)**	**24 (4.1)**	**30 (10.5)**	**25 (3.8)**
Thecoma/Fibroma	50	46	24	30	25
Thecoma	9	–	3	6	–
Fibroma	40	–	21	21	–
Others	1	–	–	3	–
Androblastoma	–	3	–	–	–
Germ cell tumor	**117 (27.9)**	**293 (47.3)**	**203 (34.8)**	**144 (50.5)**	**380 (58.5)**
Mature cystic teratoma	113	282	202	136	377
Struma ovarii	4	11	1	3	3
Mature solid teratoma	–	–	–	5	
Others	**2 (0.5)**	**2 (0.3)**	**10 (1.7)**	**–**	**–**
Total	**419 (100.0)**	**619 (99.9)**	**583 (99.9)**	**285 (99.9)**	**650 (100.0)**

[a] Patients treated at Nagoya University Hospital during 1965–1988; histologically reclassified cases, Nakashima.[27]
[b] Patients treated at Juntendo University Hospital in Tokyo during 1967–1977; histologically reclassified cases, Ishi.[28]
[c] Surgical cases examined at Department of Pathology, Tohoku University School of Medicine in Sendai during 1969–1978, Tateno.[30]
[d] Patients treated at the Los Angeles county–University of Southern California Medical Center during 1975–1985; histologically reclassified cases, Kooning.[26]

fore aging, cohort of persons born in 1945 or earlier who were alive in 1950. Thus, the accumulated tumor experience of that cohort from 1950 through 1988 disproportionately represents older ages compared to the residential populations served by university hospitals in Japan and elsewhere, that are continually being renewed by the addition of persons born each year.

For benign tumor cases, Table 7 shows that common epithelial tumors and germ cell tumors are the dominant types of benign tumors in both the Japanese and U.S. study populations, while the percentage of sex-cord stromal tumors is extremely low.[26–32)] Further, a review of the frequency of histologically-classified tumor types in each of the three ovarian tissue systems just mentioned clearly shows that, (1) among common epithelial tumors, the percentages of serous and mucinous adenocarcinoma are high in a majority of the study groups; (2) among sex-cord stromal tumors the percentage of fibroma is high ; and (3) among germ cell tumors, the percentage of mature cystic teratoma is overwhelmingly high in all of these study populations. Even though the breakdown of frequency percentage by histological tumor type varies to some extent by study population, there is a common observed pattern regarding common tumor types in each of the three tissue systems.

It is presumed that hormones, primarily estrogen and pituitary gonadotropin, affect the natural incidence of ovarian tumors, and that the tumors which commonly develop in each of the three ovarian tissue systems are those mentioned above. An interesting question is why 90% of malignant tumors, but only 60% of benign tumors, should occur in the common epithelium. Currently, a prominent pathogenetic hypothesis[33,34)] points to the ovulatory cycle, which recurs from early adolescence until menopause. To repair localized tissue damage occurring on ovary surfaces at the time of ovulation, ovarian epithelial tissues repeatedly induce cell division and recovery at damaged sites. During this process,

mutation, including events involved in transformation of an initiated cell to a cancer cell, is likely to occur in mitotic cells, with repaired epithelial tissues invaginated into the ovarian interstitium increasing sensitivity to estrogen, which is produced in the interstitium. Eventually, the combination of these factors is believed to cause the development of carcinoma.

We showed an apparent survival advantage for mucinous compared to serous cancers. However, Malkasian reported that for most histological types, observed differences in survival were more apparent than real since the behavior of different cell types was similar when compared stage for stage and grade for grade, and that mucinous cystadenomas tended to be low grade and low stage, while serous cystadenomas tended to be high grade and high stage.[35)]

In summary, more than 600 ovarian tumors in about 70,000 cohort members of Hiroshima and Nagasaki were diagnosed by the pathology review of tissue slides using the standardized classification scheme. The variations in histological types of ovarian tumors in response to radiation dose were suggested.

ACKNOWLEDGEMENTS

The Radiation Effects Research Foundation (RERF), Hiroshima and Nagasaki, Japan is a private, non-profit foundation funded by the Japanese Ministry of Health, Labour and Welfare (MHLW) and the U.S. Department of Energy (DOE) the latter through the National Academy of Sciences. This publication was supported by RERF Research Protocol RP # 2-92. This work was also supported in part by the US National Cancer Institute (NCI) contract numbers NO1-CP-71015 and NO1-CP-31012. The authors thank the doctors of both cities who gave their permission to use case information, and particularly the Tumor Registries of the Hiroshima and Nagasaki City Medical Associations, the Tissue Registries of the Hiroshima Prefectual Medical Association and Nagasaki Medical Association, Hiroshima University School of Medicine, the Research Institute for Nuclear Medicine and Biology of Hiroshima University, Nagasaki University School of Medicine, the Atomic Disease Institute of Nagasaki University School of Medicine, and many hospital and clinics of both cities. The authors would like to thank H. Moriwaki, M. Hayashi, and M. Konda for their help with data preparation and work on the tables and figures.

REFERENCES

1. Weiss, N. S., Cook, L. S., Farrow, D. C. and Rosenblatt, K. A. (1996) Ovarian cancer. In: Cancer Epidemiology and Prevention, 2nd ed., Schottenfeld, D. and Fraumeni, J. F. Jr., pp. 1040–1057, Oxford University Press, New York.
2. Parkin, D. M., Whelan, S. L., Ferlay, J., Raymond, L. and Young, J. (1997) Cancer Incidence in Five continents. Volume VII, IARC, Lyon.
3. Coleman, M. P., Esteve, J., Damiecki, P., Arslan, A. and Renard, H. (1993) Trends in cancer incidence and mortality. IARC Sci. Publ. **121**:1–806.
4. Ioka, A., Tsukuma, H., Ajiki, W. and Oshima, A. (2003) Ovarian cancer incidence and survival by histologic type in Osaka, Japan. Cancer Sci. **94**: 292–296.
5. Tamakoshi, K., Kondo, T., Yatsuya, H., Hori, Y., Kikkawa, F. and Toyoshima, H. (2001) Trends in the mortality (1950–1997) and incidence (1975–1993) of malignant ovarian neoplasm among Japanese women: analyses by age, time, and birth cohort. Gynecol. Oncol. **83**: 64–71.
6. Bristow, R. E. and Karlan, B. Y. (1996) Ovulation induction, infertility, and ovarian cancer risk. Fertil. Steril. **66**: 499–507.
7. Mori, M., Harabuchi, I., Miyake, H., Casagrande, J. T., Henderson, B. E. and Ross, R. K. (1988) Reproductive, genetic, and dietary risk factors for ovarian cancer. Am. J. Epidemiol. **128**: 771–777.
8. Preston, D. L., Shimizu, Y., Pierce, D. A., Suyama, A. and Mabuchi, K. (2003) Studies of mortality of atomic bomb survivors. Report 13: Solid cancer and noncancer disease mortality: 1950–1997. Radiat. Res. **160**: 381–407.
9. Thompson, D., Mabuchi, K., Ron, E., Soda, M., Tokunaga, M., Ochikubo, S., Sugimoto, S., Ikeda, T., Terasaki, M., Izumi, S. and Preston, D. (1994) Cancer incidence in atomic bomb survivors. Part II: Solid tumors, 1958–87. Radiat. Res. **137**: S17–S67.
10. Tokuoka, S., Kawai, K., Shimizu, Y., Inai, K., Ohe, K., Fujikura, T. and Kato, H. (1987) Malignant and benign ovarian neoplasms among atomic bomb survivors, Hiroshima and Nagasaki, 1950–80. J. Natl. Cancer Inst. **79**: 47–57.
11. Palmer, J. P. and Spratt, D. W. (1956) Pelvic carcinoma following irradiation for benign gynecological diseases. Am. J. Obstet. Gynecol. **72**: 497–505.
12. Boice, J. D. Jr., Day, N. E., Andersen, A., Brinton, L. A., Brown, R., Choi, N. W., Clarke, E. A., Coleman, M. P., Curtis, R. E., Flannery, J. T., Hakama, M., Hakulinen, T., Howe, G. R., Jensen, O. M., Kleinerman, R. A., Magnin, D., Magnus, K., Makela, K., Malker, B., Miller, A. B., Nelson, N., Patterson, C. C. and Petterson F., Pompe-Kirn, V., Primic-Zakelj, M., Prior, P., Ravnihar, B., Skeet, R. G., Skjerven, J. E., Smith, P. G., Sok, M., Spengler, R. F., Storm, H. H., Stovall, M., Tomkins, G. W. O. and Wall, C. (1985) Second cancer following radiation treatment for cervical cancer. An international collaboration among cancer registries. J. Natl. Cancer Inst. **74**: 955–975.
13. Boice, J. D. Jr., Engholm, G., Kleinerman, R. A., Blettner, M., Stovall, M., Lisco, H., Moloney, W. C., Austin, D. F., Bosch, A., Cookfair, D. L., Krementz, E. T., Latourette, H. B., Merrill, J. A., Peters, L. J., Schulz, M. D., Storm, H. H., Bjorkholm, E. Pettersson, F., Bell, J. C. M., Coleman, M. P., Fraser, P., Neal, F. E., Prior, P., Choi, W. N., Hislop, G. T., Koch, M., Kreiger, N., Robb, D., Robson, D., Thomson, D. H., Lochmuller, H., von Fournier, D., F., Frischkorn, R., Kjorstad, K. E., Rimpela, A. Pejovic, M. H., Kirn, V. P., Stankusova, H., Berrino, F., Sigurdsson, K., Hutchison, G. B. and MacMahon, B. (1988) Radiation dose and second cancer risk in patients treated for cancer of the cervix. Radiat. Res.

116: 3–55.
14. Brinkley, D. and Haybittle, J. L. (1969) The late effects of artificial menopause by x-radiation. Br. J. Radiol. **42**: 519–521.
15. Dickson, R. J. (1969) The late results of radium treatment for benign uterine hemorrhage. Br. J. Radiol. **42**: 582–594.
16. Court Brown, W. M. and Doll, R. (1965) Mortality from cancer and other causes after radiotherapy for ankylosing spondylitis. Br. Med. J. **2**: 1327–1332.
17. Darby, S. C., Doll, R., Gill, S. K. and Smith, P. G. (1987) Long term mortality after a single treatment course with X-rays in patients treated for ankylosing spondylitis. Br. J. Cancer **55**: 179–190.
18. Serov, S. F. and Scully, R. E. (1973) Histological Typing of Ovarian Tumours. No. 9, International Histological Classification of Tumours. World Health Organization, Geneva.
19. Japan Society of Obstetrics and Gynecology and the Japanese Society of Pathology: (1990) The General Rules for Clinical and Pathological Management of Ovarian Tumours. Part I. Histological Classification and Colour Atlas of Ovarian Tumours. JSOG-JSP, Tokyo.
20. Preston, D. L., Lubin, J. H., Pierce, D. A. and McConny, M. (1993) Epicure Users Guide. Hirosoft International Corporation, Seattle.
21. Young, R. and Bennett, B. (in press 2005) DS02: A revised system for atomic bomb survivor dose estimation. RERF, Hiroshima.
22. Tung, K. H., Goodman, M. T., Wu, A. H., McDuffie, K., Wilkens, L. R., Kolonel, L. N., Nomura, A. M. Y., Terada, K. Y., Carney, M. E. and Sobin, L. H. (2003) Reproductive factors and epithelial ovarian cancer risk by histologic type: a multiethnic case-control study. Am. J. Epidemiol. **158**: 629–638.
23. Ron, E., Carter, R., Jablon, S. and Mabuchi K. (1994) Agreement between death certificate and autopsy diagnoses among atomic bomb survivors. Epidemiology **5**: 48–56.
24. Scully, R. E. (1979) Tumors of the ovary and maldeveloped gonads. Atlas of Tumor Pathology, Second series, Fascicle 16. Armed Forces Institute of Pathology, Washington, D.C.
25. Yancik, R. (1993) Ovarian cancer. Age contrasts in incidence, histology, disease stage at diagnosis, and mortality. Cancer **71**: 517–523.
26. Koonings, P.P., Campbell, K., Mishell, D.R. Jr. and Grimes, D. A. (1989) Relative frequency of primary ovarian neoplasms: a 10 year review. Obstet. Gynecol. **74**: 921–926.
27. Nakashima, N., Nagasaka, T., Fukata, S., Oiwa, N., Nara, Y., Fukatsu, T. and Takeuchi, J. (1990) Study of ovarian tumors treated at Nagoya University Hospital, 1965–1988. Gynecol. Oncol. **37**: 103–111.
28. Ishi, K., Yamada, T., Nakamura, A., Saito, O. and Hashimoto, T. (1977) Clinicopathological analysis of malignant ovarian tumors. Japan J. Clin. Pathol. **25**(Suppl.): 537. (in Japanese)
29. Sasano, N., Tateno, H., Takano, A. and Okuno, Y. (1983) Ovarian cancers in Miyagi prefecture, Japan. In: Stalsberg H. An international survey of distributions of histologic types of tumours of the testis and ovary. Technical Report Series, Vol. 75, pp. 193–198, UICC, Geneva.
30. Tateno, H. and Sasano, N. (1983) Ovarian tumours in Sendai, Japan. General hospital material. In: Stalsberg, H. An international survey of distributions of histologic types of tumours of the testis and ovary. Technical Report Series, Vol. 75, pp. 291–296, UICC, Geneva.
31. Beck, R. P. and Latour, J. P. A. (1960) Review of 1019 benign ovarian neoplasms. Obstet. Gynecol. **16**: 479–82.
32. Katsube, Y., Berg, J. W. and Silverberg, S. G. (1982) Epidemiologic pathology of ovarian tumors: A histopathological review of primary ovarian neoplasms diagnosed in the Denver Standard Metropolitan Statistical Area, 1 July–31 December 1969 and 1 July–31 December 1979. Int. J. Gynecol. Pathol. **1**: 3–16.
33. Cramer, D. W. and Welch, W. R. (1983) Determinants of ovarian cancer risk. II. Inferences regarding pathogenesis. J. Natl. Cancer Inst. **71**: 717–721.
34. Godwin, A. K., Testa, J. R. and Hamilton, T. C. (1993) The biology of ovarian cancer development. Cancer **71**: 530–536.
35. Malkasian, G. D., Melton, III J., Brien, P. C. and Green, MH. (1984) Prognostic significance of histologic classification and grading of epithelial malignanancies of the ovary. Am. J. Obstet. Gynecol. **149**: 274.

Received on September 12, 2005
Revision received on December 20, 2005
Accepted on January 23, 2006